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Role of Estrogens and Androgens in Osteoporosis

Michaël R Laurent, University Hospitals Leuven, Leuven, Belgium

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Introduction

Osteoporosis is a skeletal disease characterized by compromised bone strength, which predisposes a person to an increased risk of fracture (NIH Consensus Development Panel on Osteoporosis Prevention Diagnosis and Therapy, 2001). Bone strength is determined not only by bone mineral density (BMD) but also by bone size and macroarchitecture (particularly cortical bone area, but also cortical thickness and trabecular bone volume), microarchitectural features such as cortical porosity, trabecular thickness and perforations, as well as bone material properties (Seeman and Delmas, 2006).

As early as the 1940s, estrogen deficiency was blamed for post-menopausal osteoporosis and androgen deficiency for male osteoporosis (Albright *et al.*, 1941). However, by the late 1990s it was realized that estrogens also played an important role in the pathophysiology of male osteoporosis, and estrogens were even implicated in bone loss in old age as well as age-related secondary hyperparathyroidism (Riggs *et al.*, 1998). More recently however, there is growing awareness that aging has an independent and overriding influence on bone loss and fractures in both genders. Indeed, there is an exponential increase in fracture risk in elderly of both genders (see section “Fractures”) resulting not only from an increasing risk of falls (Riggs *et al.*, 2006) but also from distinctive mechanisms of age-related bone loss such as oxidative stress, cellular senescence, hypercortisolism etc. (Farr *et al.*, 2017; Khosla *et al.*, 2011a; Khosla *et al.*, 2011b; Manolagas, 2010; Ucer *et al.*, 2017).

The aim of this chapter is to provide an overview of how estrogens, androgens and their receptors influence skeletal development and maintenance. However, their effects are gender-specific (estrogens play a key role in both genders whereas androgens may provide some additional benefit in young men), time-specific (i.e. due to enhanced development of peak bone mass, prevention of bone loss later in life, or both), compartment-specific (i.e. different in cortical vs. trabecular bone; see Table 1) and dose-dependent (i.e. estrogen levels below certain thresholds are associated with bone loss, whereas supraphysiological sex steroid levels generally confer no added skeletal benefits). Thus, to understand the role of sex steroids, we will first outline the effects of age and gender on cortical and trabecular bone as well as fracture risk.

Gender Differences in Bone Development, Bone Loss and Fracture Risk

Fractures

Gender is a key clinical risk factor for fractures, second only to age. The lifetime risk of osteoporotic fractures after the age of 50 years is as high as 45%–55% in women, compared to 20%–25% in men in high-risk Caucasian populations (Ahmed *et al.*, 2009; Lippuner *et al.*, 2009; Nguyen *et al.*, 2007). Also for hip fractures, the male: female incidence ratio is about 1:2 and remarkably constant worldwide despite > 10-fold geographic differences in fracture incidence (Kanis *et al.*, 2012). Still, this means that men account for about one-third of the 9 million osteoporotic fractures worldwide, with some gender differences according to the fracture site (men accounting for 30% of hip and 39% of spine fractures, only 25% of humerus and 20% of forearm fractures, but 54% at other sites e.g. ribs) (Barrett-Connor *et al.*, 2010; Johnell and Kanis, 2006).

Fracture incidence starts to increase around the age of menopause in women, and then further accelerates in parallel in both genders after the age of 70 years (Fig. 1) (Bergström *et al.*, 2008; Curtis *et al.*, 2016; Laurent *et al.*, 2013). The gender difference in fracture risk can be explained by musculoskeletal sexual dimorphism i.e. the fact that men develop greater bone and muscle mass during puberty and adulthood, and do not experience accelerated bone loss after midlife as post-menopausal women do.

Table 1 Summary of the time-, gender- and compartment-specific (cortical vs. trabecular bone) effects of estrogens and androgens

	Estrogens				Androgens			
	Cortical bone Women	Men	Trabecular bone Women	Men	Cortical bone Women	Men	Trabecular bone Women	Men
PBM	++	++	++	+	–	+	?	+
Midlife	–	–	–	–	–	–	–	–
Old age	++	++	++	++	–	–	–	–

++ = very important role, + = important role, ? = uncertain role, – = no established role.

Fig. 1 Age- and sex-specific incidence rates of any fractures among adults in the United Kingdom, between 1988 and 2012, based on data from the Clinical Practice Research Datalink. Reproduced, with permission, from [Curtis et al. \(2016\)](#).

Fig. 2 (A) Cortical bone area at the tibia and (B) trabecular number at the distal radius, at the approximate ages of peak bone mass, middle age and in old age (20, 50 and 90 years, respectively), in men (dark gray) and women (light gray). Adapted and reproduced, with permission, from [Khosla et al. \(2006b\)](#) and [Lauretani et al. \(2008\)](#).

Cortical and Trabecular Bone Development and Maintenance

The structural development and maintenance of the skeleton can be divided into three phases: peak bone mass (PBM) acquisition, midlife, and old age. Men between 20 and 30 years have about 25% greater bone mass (whole body bone mineral content, BMC) ([Boot et al., 2010](#)). However, this is not surprising given the fact that men are on average 8% taller than women (because dual-energy X-ray absorptiometry is a projectional technique and in 3D, $1.08^3 \approx 1.25$) ([Almeida et al., 2017](#)). Gender differences in PBM are however not uniform, but time- and site-specific (e.g. PBM is reached earlier at the hip than at the spine). More importantly, these differences are explained almost entirely by the fact that young men develop *wider* cortical bone diameters, even after adjustment for height ([Baxter-Jones et al., 2011](#); [Berger et al., 2010](#); [Henry et al., 2004](#); [Lorentzon et al., 2005](#); [Walsh et al., 2009](#)). Other determinants of bone strength also show sexual dimorphism ([Almeida et al., 2017](#)) but the key determinant is bone width. The latter is determined by periosteal expansion and offers important biomechanical advantages, because bone strength scales to the fourth power with bone diameter. In fact, young men have similar cortical thickness as women, slightly lower cortical volumetric BMD, greater cortical porosity and lower trabecular bone volume in the spine, but these elements are outweighed entirely by greater cortical bone size ([Berthold et al., 2006](#); [Burt et al., 2016](#); [Hansen et al., 2014](#); [Khosla et al., 2006b](#); [Kirmani et al., 2009](#); [Macdonald et al., 2011](#); [Nishiyama et al., 2012](#); [Riggs et al., 2004](#)).

Midlife may be a period during which men continue to consolidate their cortical bone assets. Trabecular bone volume declines early after PBM in both genders, but in men, some studies suggest that this is mainly due to loss of trabecular thickness (which is biomechanically less deleterious). Thus, both cortical bone cross-sectional area and trabecular number increase towards midlife in men, whereas they slightly decline in women ([Fig. 2](#)) ([Khosla et al., 2006b](#); [Lauretani et al., 2008](#); [Riggs et al., 2008](#)). What drives these changes remains incompletely understood, but they occur independently of changes in sex steroids.

After menopause and in aging however, two pathophysiological alterations disturb the remodeling process (i.e. the resorption of bone by osteoclasts and bone formation at previously resorbed sites by osteoblasts). Collectively, the activities of these cells are coupled in basic multicellular units (BMUs). The first disturbance is an increased bone turnover with an increased number of BMUs. As a result, there are more osteoclasts resorbing pits at any given moment throughout the skeleton, even though osteoclast activity within each BMU is not more vigorous ([Szulc and Seeman, 2009](#)). Secondly, the osteoblasts in these BMUs fail to completely refill the resorption cavity. This leads to a small deficit in bone formation compared to resorption, which is amplified by the increased number of remodeling cycles. At the structural level, these two pathophysiological processes results in trabecular thinning and eventually

perforations and loss of trabecular number, widening of the medullary cavity with trabecularization of the cortex and increased cortical porosity. All of these structural features of skeletal decay are exaggerated in women compared to men (Fig. 2), in association with their greater bone turnover and lower estrogen levels after menopause (Khosla *et al.*, 2006a; Khosla *et al.*, 1998; Riggs *et al.*, 2006; Riggs *et al.*, 2004; Riggs *et al.*, 2008). Indeed, there is no “andropause” equivalent, and older men generally have higher serum estrogen concentrations than post-menopausal women. Periosteal expansion continues into old age and appears to represent a compensatory mechanism for bone loss from endosteal resorption (Pye *et al.*, 2017). This explains why periosteal apposition in old age may be even higher in women, nevertheless the net balance between endosteal resorption and periosteal expansion is more negative in women, leading to greater cortical thinning (Ahlborg *et al.*, 2013; Seeman, 2002; Zebaze *et al.*, 2010).

In conclusion, male gender is a protective factor that approximately halves the lifetime risk of osteoporotic fractures by both increasing PBM and decreasing subsequent bone loss. In the next section, we will discuss how sex steroids contribute to these gender differences.

Effects of Sex Steroids on Cortical and Trabecular Bone

Endogenous androgens and estrogens are C19 and C18 steroid hormone ligands of the androgen receptor (AR) and estrogen receptors (ER α and ER β), respectively. Testosterone (T), the principal circulating androgen, can be converted by 5 α -reductase enzymes to the more potent androgen dihydrotestosterone (DHT), and by the aromatase enzyme (CYP19A1) to 17 β -estradiol (E2), the principal ligand of ER α . Thus, T has a dual mode of action, both androgenic as well as estrogenic.

Role of the Estrogen Receptors (ER α and ER β)

Clinical evidence

Before bisphosphonates became available, estrogen replacement therapy together with calcium- and vitamin D-supplementation constituted the only therapeutic option for osteoporosis in post-menopausal women. Similarly, young men with hypogonadotropic hypogonadism are at increased risk for osteoporosis, which is reversible by T replacement therapy (Finkelstein *et al.*, 1987). Furthermore, surgical or pharmacological castration e.g. for breast or prostate cancer increases the risk of osteoporosis and fractures (Greenspan *et al.*, 2013; Hamilton *et al.*, 2010; Shahinian *et al.*, 2005). However, since hormone deficiency or deprivation results in both androgen as well as estrogen deficiency, the respective contributions of androgen- or estrogen-receptor signaling cannot be distinguished. Nevertheless, selective estrogen-receptor modulators (SERMs) are antiresorptive in men with low E2 levels (Uebelhart *et al.*, 2004), and prevent fractures in men receiving androgen deprivation therapy for prostate cancer, attesting to the importance of estrogen signaling even in men (Smith *et al.*, 2013). Also in male-to-female transsexuals, pharmacological E2 prevents bone loss, even despite androgen suppression (Lapauw *et al.*, 2008; Mueller *et al.*, 2011; Ruetsche *et al.*, 2005).

A more direct way of examining this issue is by animal or human models with genetic receptor or enzyme dysfunctions, discussed in the next paragraph. However, it is important to note that all of the effects in these knock-out animal models may be developmental, even though some phenotypes manifest at older age. Nevertheless, also after skeletal maturity, aromatase inhibition in adult animals or humans results in bone loss not only in women but also in men which cannot be compensated by AR actions alone (Falahati-Nini *et al.*, 2000; Finkelstein *et al.*, 2016; Leder and Finkelstein, 2005; Vanderschueren *et al.*, 2000). Finally, a large number of epidemiological studies (reviewed in Vanderschueren *et al.*, 2014) show that free or bioavailable E2 levels, are associated with bone loss and fracture risk in older men.

Genetic studies

Case reports of severe osteoporosis in men or women with aromatase or ER α deficiency attest to the importance of estrogens for bone health (Bilezikian *et al.*, 1998; Quaynor *et al.*, 2013; Smith *et al.*, 1994; Taes *et al.*, 2009). Notably, periosteal circumference was normal in an ER α KO man, supporting a role for the AR in periosteal bone formation (Smith *et al.*, 2008). Also in population studies, polymorphisms in the *ESR1* (ER α), *CYP19A1* (aromatase) or *COMT* (an estrogen-metabolizing enzyme) gene are associated with bone mass or fracture risk (Eriksson *et al.*, 2008; Gennari *et al.*, 2004; Limer *et al.*, 2009; Paternoster *et al.*, 2013; Van Pottelbergh *et al.*, 2003). In young rodent models, aromatase knock-out results in severely disturbed cortical and trabecular bone acquisition in both genders, despite increased T and IGF-1 levels (Matsumoto *et al.*, 2006; Öz *et al.*, 2001). In ER α KO mice, cortical bone development is impaired in both genders. Trabecular bone volume is also decreased by ER α KO in females but normal or even paradoxically increased in males, because of hypothalamic-pituitary feedback and high androgen levels signaling through the AR (Lindberg *et al.*, 2002; Sims *et al.*, 2003; Vidal *et al.*, 2000).

In female rodent models, ER β seems to have a weaker opposite, inhibitory role on the stimulatory effects of ER α (Nicks *et al.*, 2016; Windahl *et al.*, 2001; Windahl *et al.*, 1999). However, any role for ER β in males or in humans remains unconfirmed (Almeida *et al.*, 2017). G protein-coupled receptor 30 (GPR30) has also been proposed as an ER (and therefore renamed G protein-coupled ER 1 or GPER1), although this remains controversial. In any case, GPR30 appears redundant for the effects of estrogens on cortical and trabecular bone, although it may play a role at the growth plate (Vanderschueren *et al.*, 2014).

In summary, estrogens are indispensable for normal cortical and trabecular development as well as maintenance, not only in women but also in men (Table 1).

Target cells and genes

To identify whether the target cells for these effects of estrogens are osteoclasts, osteoblasts, osteocytes or other cell types, conditional KO models using Cre/LoxP technology have been used, in which ERs or AR can be deleted in specific cell types (Davey *et al.*, 2004). Based on such models, estrogens appear to stimulate cortical thickness through ER α in the osteoblast cell lineage in female mice, although only transiently in male mice (Almeida *et al.*, 2013; Määttä *et al.*, 2013a; Melville *et al.*, 2014). In female mice, it remains debated whether trabecular bone volume is maintained through actions of ER α in either osteoclasts (Almeida *et al.*, 2013; Martin-Millan *et al.*, 2010; Nakamura *et al.*, 2007; Seitz *et al.*, 2012) or osteoblasts and osteocytes (Kondoh *et al.*, 2014; Määttä *et al.*, 2013a; Melville *et al.*, 2014; Windahl *et al.*, 2013a). In male mice, the effect of estrogens on trabecular bone is not mediated via osteoclasts, but possibly via late osteoblasts or osteocytes (although not osteoblast precursor cells) (Määttä *et al.*, 2013a; Ucer *et al.*, 2015; Windahl *et al.*, 2013a).

The downstream actions of ER α can be mediated in four different ways. Firstly, translocation to the nucleus and regulation of target genes by direct binding to estrogen response elements (ERE), which are specific DNA sequences recognized by the ER α . This classical mode of action requires pioneer factors which modulate chromatin availability (such as GATA4; Miranda-Carboni *et al.*, 2011) and co-activators, of which SRC-1 is the best-known example. As a consequence, trabecular bone loss in SRC-1 knock-out mice is due to estrogen resistance in females and androgen resistance in males (Mödder *et al.*, 2004; Yamada *et al.*, 2004). Secondly, sex steroid receptors (both ER α and AR) may bind and influence (positively or negatively) the signaling of other transcription factors, e.g. NF- κ B, AP-1 or RUNX2 (Baniwal *et al.*, 2009; Martin *et al.*, 2015; McCarthy *et al.*, 2003). Thirdly, both of the previous two (direct and indirect) genomic signaling mechanisms may be mediated by the unliganded ER α (but not the AR), and this ligand-independent effect can stimulate or repress gene expression (Almeida *et al.*, 2013; Rudnik *et al.*, 2008). Fourthly, both liganded ER α and AR may stimulate kinase-mediated extranuclear signaling at the plasma membrane, which is called non-genomic (or non-genotropic) signaling (Kousteni *et al.*, 2001; Kousteni *et al.*, 2002; Kousteni *et al.*, 2003). Knock-in mouse models in which the AR or ER are replaced by a mutant incapable of DNA binding demonstrate the physiological consequence of this mode of action, although these effects are modest and usually opposite to the classical genomic effects (Almeida *et al.*, 2010; Pang *et al.*, 2012; Syed *et al.*, 2011; Syed *et al.*, 2007; Syed *et al.*, 2005). The latter mode of action is involved in the ER α regulation of cortical bone mass and its regulation of oxidative stress in bone cells and their mechanoresponsiveness (see below) (Manolagas, 2010). An E2 dendrimer conjugate which selectively stimulates extranuclear estrogen signaling maintains protective effects on cortical bone without stimulating the uterus (Bartell *et al.*, 2013; Farman *et al.*, 2017), which supports further drug development selectively exploiting this pathway.

The direct target genes of ER α in osteoblasts, and even more so in osteoclasts or the target genes of AR in any target cell, remain poorly understood (Krum, 2011). Many target genes have been proposed, but few have been extensively validated (Almeida *et al.*, 2017; Vanderschueren *et al.*, 2014). Recent studies suggest that estrogens stimulate osteoblast expression and cleavage of Fas ligand to induce anti-resorptive effects via pre-osteoclast apoptosis, while other studies suggest involvement of SDF-1 (also known as Cxcl12) (Garcia *et al.*, 2013; Krum *et al.*, 2008; Ucer *et al.*, 2017; Wang *et al.*, 2015).

Rodent studies have suggested that female ER α KO mice also have an altered bone formation response to mechanical loading (Lee *et al.*, 2003). However, this seems to be a ligand-independent effect of ER α , while ER α KO in male mice, gonadectomy or ARKO has the opposite effect i.e. enhanced skeletal mechanoresponsiveness (Callewaert *et al.*, 2010a; Saxon *et al.*, 2012; Sinnesael *et al.*, 2015b; Windahl *et al.*, 2013b). Whether the altered mechanoresponsiveness in these models is explained by altered bone turnover (Vanderschueren *et al.*, 2014), altered background physical activity or whether these findings are generalizable to humans, remains unknown.

Collectively, these studies suggest that ER α actions are important for cortical and trabecular bone development in both genders, although more work is needed to fully elucidate the target cell(s) and molecular mechanisms of these effects.

Role of the Androgen Receptor (AR)

Rodent studies have demonstrated that androgens stimulate periosteal bone expansion in growing animals and have antiresorptive effects on trabecular bone through a direct effect of AR and independent of aromatization (Beck *et al.*, 2014; Movérare *et al.*, 2003; Venken *et al.*, 2006). In contrast to the strikingly osteopenic phenotypes resulting from selective estrogen deficiency, studies in androgen-insensitive or AR knock-out (ARKO) rodents reveal a milder cortical and trabecular bone phenotype (Callewaert *et al.*, 2009; Kawano *et al.*, 2003; MacLean *et al.*, 2008; Venken *et al.*, 2006; Yeh *et al.*, 2002), which is quite normal compared to female reference values. The same probably applies to XY women with androgen insensitivity syndrome, although less studies are available (Han *et al.*, 2008). Also in the general population, polymorphisms which negatively influence AR signaling such as long CAG repeats, have been not been negatively associated with male bone mass—in fact in some studies, a positive association due to hypothalamic-pituitary feedback and increased estrogen actions has been observed (Huhtaniemi *et al.*, 2009). In other words, androgens are responsible for the greater cortical bone expansion and trabecular PBM seen in young adult males compared to females, but they are not indispensable for normal cortical and trabecular bone development as estrogens are.

More recent cell-specific ARKO models have suggested that the effect of androgens on trabecular bone development is, at least partly, mediated through effects of the AR in osteoblasts and osteocytes. There is some evidence that the AR in osteoblasts enhances trabecular bone mass in female mice (Määttä *et al.*, 2013b), but whether or to what extent androgens promote bone mass in women (e.g. with hyperandrogenism due to polycystic ovary syndrome) remains unknown. Most likely, the effect of

androgens on trabecular bone involves reduced bone resorption, rather than an anabolic or increased bone formation effect (Chiang *et al.*, 2009; Notini *et al.*, 2007; Sinnesael *et al.*, 2013; Ucer *et al.*, 2015). The expression of the AR in osteoclasts as well as any direct contribution thereof to the antiresorptive effect of androgens remains questionable (Sinnesael *et al.*, 2015a; Ucer *et al.*, 2015). Remarkably, the key effect of androgens on periosteal bone expansion does not appear to be mediated by the AR in osteoblast-lineage cells either (Ucer *et al.*, 2015).

Hence, the quest to identify the—extraskeletal—target cell(s) responsible for the effect of androgens on cortical bone remains open. Although the AR exerts well-known anabolic actions on muscle, which may in turn positively influence bone mass, the effects of androgens on bone are certainly not entirely explained by muscle-bone interactions (Laurent *et al.*, 2016a; Laurent *et al.*, 2016c).

Similarly, it is known that rising serum T during early puberty in males indirectly regulate growth hormone and insulin-like growth factor 1 (IGF1) levels, which may partially (but not fully) explain the periosteal bone expansion induced by androgens in early puberty (Callewaert *et al.*, 2010b). The perinatal T surge on the other hand is a major regulator of pubertal growth hormone secretion and ultimate height, but it appears redundant for the inhibition of trabecular bone resorption and periosteal expansion induced by androgens (Sims *et al.*, 2006). Finally, there is some evidence that low IGF1 may contribute to fracture risk as well as frailty in older men (Boonen *et al.*, 2002; Ohlsson *et al.*, 2011). Still, the role of the somatotrophic axis, by itself as well as its contribution to the effects of sex steroids in male or female osteoporosis, remain poorly understood.

Whether inducible AR deletion at later age has any direct detrimental skeletal effects in skeletally mature mice, remains yet unanswered. This is an important topic for future research because a direct role of androgens in the development of osteoporosis in older men has not been confirmed (Finkelstein *et al.*, 2016; Idan *et al.*, 2010; Laurent *et al.*, 2015). However, some epidemiological studies suggest that the combination of low serum E2 and T may be associated with higher fracture risk than low E2 alone (Amin *et al.*, 2006; Woo *et al.*, 2012). Although androgens may have a minor independent effect on bone turnover markers (Khosla, 2015), on risk of falls and fractures independent of BMD (Khosla, 2010; Meier *et al.*, 2008; Orwoll *et al.*, 2006), and on trabecular bone in the spine of mice treated with strong AR antagonists (Wu *et al.*, 2016), clearly more research is needed.

In summary, the beneficial skeletal effects of androgens mainly arise during puberty, by establishing greater trabecular PBM and greater radial bone expansion in young men. On the other hand, an independent effect of androgens in older men remains hitherto unconfirmed (Table 1). The development of osteoporosis in older men is mainly associated with estrogen deficiency, especially when serum T concentrations fall below 200 ng/dL and consequently, E2 serum levels below 10 pg/mL (Finkelstein *et al.*, 2016).

Other Players in the Gonadotropic Axis: SHBG and FSH

T, DHT and E2 are bound with high affinity to sex hormone-binding globulin (SHBG) and non-specifically to bulk carrier proteins such as albumin. Consequently, only about 1%–5% of these active sex steroids circulate freely i.e. not bound to proteins. According to the free hormone hypothesis however, this small percentage constitutes the active sex steroid because only non-protein-bound hormones are proposed to diffuse across cell membranes to activate their nuclear receptors. Calculated or measured free T or E2 concentrations are often used in clinical practice as well as in studies related to osteoporosis, although many fundamental and practical concerns surround this approach (Laurent and Vanderschueren, 2014). Nevertheless, numerous studies show that higher SHBG levels are associated with greater BMD and cortical bone size in young men, but higher bone loss and fracture risk in older men and post-menopausal women (Cawthon *et al.*, 2016; Eriksson *et al.*, 2006; Hsu *et al.*, 2015; Hsu *et al.*, 2016; Lee *et al.*, 2008; Mellström *et al.*, 2008; Nielson *et al.*, 2017; Vanbillemont *et al.*, 2010; Vandenput *et al.*, 2016; Vanderschueren *et al.*, 2014). This may be explained by the fact that SHBG is sensitive metabolic marker rather than by its effect on free sex steroids, given the lack of a bone phenotype in SHBG-transgenic mice (Laurent *et al.*, 2016b).

Finally, there are experimental animal studies suggesting that increased follicle-stimulating hormone (FSH) levels per se contribute to (peri-)menopausal bone loss, although this remains controversial and evidence in humans remains limited (Allan *et al.*, 2010; Sun *et al.*, 2006; Zhu *et al.*, 2012).

Role of Estrogens and Androgens in the Diagnosis and Treatment of Osteoporosis

Role of Sex Steroids in Osteoporosis Work-Up

The role of sex steroids in the diagnosis of osteoporosis is generally limited. Osteoporosis is most commonly a disorder of post-menopausal women. Although all post-menopausal women have low E2 concentrations, those with the lowest serum E2 levels have the lowest cortical and trabecular volumetric BMD and the highest fracture risk (Khosla *et al.*, 2005; Lee *et al.*, 2008). However, there is no clinical utility of E2 or SHBG measurements in post-menopausal women, neither for fracture risk assessment nor to predict benefits of osteoporosis therapies, even in hormone-replacement therapy (Crandall *et al.*, 2015).

In contrast to post-menopausal women, most aging men retain relatively normal serum T concentrations, although free or bioavailable T concentrations decline more substantially because SHBG increases in older men (Bhasin *et al.*, 2011; Jardi *et al.*, 2018). Although low E2 and high SHBG (particularly at a threshold < 16 pg/mL total E2 or < 12 pg/mL of bioavailable E2 (Amin *et al.*, 2000; LeBlanc *et al.*, 2009; Mellström *et al.*, 2008; Woo *et al.*, 2012)) are associated with greater fracture risk in older men, the

clinical utility of measuring these sex steroids in older men is limited (Orwoll *et al.*, 2017). Still, current guidelines recommend measuring serum T concentrations in the work-up for male osteoporosis (Watts *et al.*, 2012). This may be useful in younger men with unexplained “idiopathic” osteoporosis, while it may have little usefulness in a geriatric population.

Sex Steroid Receptors as Treatment Targets in Osteoporosis

Estrogen replacement therapy

Since the Women's Health Initiative study, estrogen-replacement therapy (colloquially known as hormone replacement therapy, HRT) is no longer broadly recommended for the prevention of chronic diseases including osteoporosis in post-menopausal women, due to an increased risk of breast cancer, dementia, gallbladder disease, stroke, deep vein thrombosis (DVT), pulmonary embolism and urinary incontinence (Manson *et al.*, 2013). However, HRT is still a first-line treatment option for vasomotor symptoms. Excess adverse events were mainly observed with combination HRT with conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA). CEE alone still increased the risk of stroke, DVT, gallbladder disease and urinary incontinence relative to placebo, although mainly in older women. In women aged 50–59 years however, the risk/benefit ratio was favorable (Manson *et al.*, 2013).

Both CEE and CEE + MPA significantly prevented hip fractures (–33% for both groups), vertebral fractures (–36% and –32% respectively) and total fractures (–28% and –24% respectively) (Manson *et al.*, 2013). In general however, HRT is not recommended for fracture prevention per se, given the availability of more effective treatments with less side-effects, such as bisphosphonates (Recker *et al.*, 2007). Nevertheless, in women with low or moderate fracture risk who use HRT for vasomotor symptoms, another antiresorptive therapy may not be required as long as HRT is continued. However, post-menopausal women at high risk for fractures should be treated with osteoporosis drugs such as bisphosphonates (Almeida *et al.*, 2017).

Selective estrogen receptor modulators (SERMs)

SERMs such as tamoxifen, raloxifene, bazedoxifene and lasofoxifene bind to the ER α ligand binding pocket and are thus estrogen antagonists in the presence of E2 and partial agonists in the absence of estrogens. Thus, they induce bone loss in premenopausal women but prevent bone loss in post-menopausal women. Notably, SERMs have tissue-specific effects: they have beneficial agonistic effects on bone and desirable antagonistic effects on breast tissue, but unwanted antagonistic vasomotor effects and adverse agonistic effects on the liver (promoting venous thromboembolism) and (in case of tamoxifen only) on the uterus. This tissue-specificity is explained by tissue-specific differences in recruitment of ER α co-activators and co-repressors (Shang and Brown, 2002). Full agonism of ER α requires two co-activator interaction surfaces, called activation function (AF)-1 and 2. The bulky side-chain of SERMs hinders approximation of helix 12 and recruitment of co-activators to AF-2, which is situated in the ligand-binding domain (Almeida *et al.*, 2017). Tissue-specificity is further determined by AF-1, which is situated on the ER α aminoterminal domain. Mice lacking ER AF-1 display a normal response to E2 in the liver and almost full responsiveness in cortical bone, but no response in trabecular bone and only weak effects on the uterus (Börjesson *et al.*, 2011). All available SERMs, as well as non-nuclear ER agonists such as estrogen dendrimer conjugate require a functional AF-1 (Börjesson *et al.*, 2013; Börjesson *et al.*, 2016; Farman *et al.*, 2017). Interestingly, ICI 182,780 (a potent ER α antagonist) works as an agonist on trabecular bone and on the uterus of ovariectomized ER α AF-2 null mice (Moverare-Skrtic *et al.*, 2014). Further work is needed to develop compounds that selectively exploit beneficial ER α effects on bone without unwanted effects on other organs.

Randomized trials have demonstrated that SERMs prevent vertebral fractures (Cummings *et al.*, 2010; Ettinger *et al.*, 1999; Silverman *et al.*, 2008). Lasofoxifene additionally reduces non-vertebral fractures as well as coronary heart disease and stroke (Cummings *et al.*, 2010), while for raloxifene and bazedoxifene only post-hoc analyses suggest prevention of non-vertebral fractures in high-risk subgroups (Delmas *et al.*, 2003; Silverman *et al.*, 2012). Hip fracture prevention has not been demonstrated however, and for bazedoxifene evidence of breast cancer chemoprophylaxis is lacking. In clinical practice, raloxifene or lasofoxifene may be useful in relatively young post-menopausal osteoporotic women with low risk of hip fractures or venous thromboembolism, or in women with contraindications to other drugs (Almeida *et al.*, 2017).

As mentioned above, SERMs appear to exert similar effects in men with severe hypogonadism and compromised E2 levels (Doran *et al.*, 2001; Uebelhart *et al.*, 2004), however they are not approved for men. In randomized trials, raloxifene and toremifene also reduced bone turnover and increased BMD in men receiving androgen-deprivation therapy for prostate cancer, while toremifene reduced incident vertebral fractures (Smith *et al.*, 2004; Smith *et al.*, 2013). However, due to an increased risk of venous thromboembolism, SERMs are not currently approved for this indication either (Alibhai *et al.*, 2017).

Testosterone

Several randomized trials have examined the effects of T therapy in post-menopausal women. Although a significant improvement in sexual function has been suggested by a recent meta-analysis, a deleterious effect on lipid profiles, increased risk of acne and hirsutism, and no effect on BMD was found, while long-term safety data remain lacking (Elraiyah *et al.*, 2014).

In recent years, there has been a tremendous increase in the prescription of T for adult or older men in some countries, particularly in the United States. While T replacement therapy has established benefits in men with congenital or acquired hypogonadism (Basaria, 2014; Finkelstein *et al.*, 1989), its use in so-called “late-onset hypogonadism” is much more controversial. Notably, the definition of a clinical syndrome associated with “low T” levels in older men remains controversial. According to the

European Male Aging Study criteria of total $T < 11$ nmol/L, free $T < 220$ pmol/L and at least three sexual symptoms, only 3.2% of men 60–69 years and 5.1% of those 70–79 years would classify as late-onset hypogonadism (Wu *et al.*, 2010). Secondly, not only adverse effects on the prostate but particularly adverse cardiovascular events have drawn much attention (Basaria *et al.*, 2010; Budoff *et al.*, 2017). The stimulatory effects on the prostate may be blunted by concomitant 5 α -reductase inhibitors, without affecting the musculoskeletal benefits (Amory *et al.*, 2004; Bhasin *et al.*, 2012; Borst *et al.*, 2014; Matsumoto *et al.*, 2002).

T therapy has produced significant but modest BMD increases in some randomized trials (Amory *et al.*, 2004; Kenny *et al.*, 2010; Nair *et al.*, 2006) but not others (Christmas *et al.*, 2002; Emmelot-Vonk *et al.*, 2008; Snyder *et al.*, 1999). The benefits of T appeared limited to men with baseline low T levels and treated for longer duration with T at relatively high doses, with possibly greater effectiveness of i.m. injections (Borst and Yarrow, 2015; Giannoulis *et al.*, 2012; Snyder *et al.*, 1999; Tracz *et al.*, 2006).

More recently, the Testosterone Trials investigated the efficacy and safety of T therapy in men with late-onset hypogonadism. After 1 year, transdermal T increased the primary outcome of spine trabecular volumetric BMD by QCT by 6.8%. Additional significant increases were seen on femoral and spine cortical and trabecular bone and estimated strength; the effect was greater on trabecular than on cortical bone, and greater on the spine than on the hip (Snyder *et al.*, 2017). T gel increased lumbar spine areal BMD by only 1.2%, while femoral BMD was not significantly affected. Importantly however, evidence that T reduces fractures remains lacking. Therefore, current guidelines in male osteoporosis recommend that hypogonadal men with low T and low fracture risk may not need additional anti-osteoporotic medications, while men at increased fracture risk should be treated with approved fracture prevention drugs (Watts *et al.*, 2012).

Selective androgen receptor modulators (SARMs)

In contrast to the well-established tissue-specific agonistic/antagonistic effects of SERMs, the development of SARMs has been largely disappointing. Notably, SARMs maintain anabolic effects on bone and muscle with less agonistic effects on reproductive organs, but true tissue-specificity has hitherto not been demonstrated (Dubois *et al.*, 2012; Dubois *et al.*, 2015). Most SARMs cannot be converted to DHT, which may well explain why their deleterious effect on the prostate is diminished (but often not completely absent); they can be regarded more as “marginators” (greater dose-dependent margin between wanted and unwanted effects) than as true modulators (Almeida *et al.*, 2017). Unfortunately, SARMs are not aromatizable either, which is problematic given the key role of estrogens for osteoporosis in older men. In a randomized trial, DHT treatment in older men reduced BMD, probably because gonadotropins and E2 were concomitantly suppressed (Idan *et al.*, 2010). These results are in line with the Hypogonadism and Estrogen Removal (HER) trial, which has shown that the effects of T on cortical and trabecular bone and bone turnover in older men depends largely if not exclusively on estrogens (Finkelstein *et al.*, 2016). Despite beneficial effects in hypogonadal animal studies, few clinical trials with SARMs are available, and none have demonstrated positive effects on BMD (Dalton *et al.*, 2011; Dobs *et al.*, 2013; Papanicolaou *et al.*, 2013). Furthermore, the potential cardiovascular side-effects of T raise concern for further SARM development. Nevertheless, other therapies which could reverse muscle and bone loss (i.e. concomitant osteoporosis and sarcopenia) in elderly of both genders are eagerly awaited (Laurent *et al.*, 2016a).

Summary

At PBM, men develop wider bones due to greater periosteal bone expansion, as well as greater trabecular bone mass. Estrogens are essential for cortical and trabecular bone development in both genders; however, key elements of musculoskeletal sexual dimorphism are determined by androgen effects of periosteal bone formation and trabecular bone resorption. During midlife, men continue to consolidate their cortical and trabecular bone assets, likely independent of sex steroids. Cortical and trabecular bone loss with aging however is dependent on estrogen deficiency in post-menopausal women, as well as in some men (particularly those with serum $T < 200$ ng/dL and $E2 < 10$ pg/mL) and high SHBG. Although the clinical role of sex steroids in the diagnosis and treatment of osteoporosis in general is limited, there is growing interest and attention for bone loss and fracture risk in patients treated with hormone deprivation therapies for breast and prostate cancer. Further research is needed to investigate the cellular and molecular mechanisms by which sex steroid regulate bone metabolism, which could potentially lead to the development of new drugs to exploit their musculoskeletal benefits without adverse reproductive or cardiovascular effects.

See also: Estrogen and the Male. Human Aromatase Deficiency. Hypogonadism and Testosterone Therapy in Elderly Men. Reproductive and Nonreproductive Actions of Testosterone

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